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Activation of AMPK by metformin protects infarcted myocardium through suppression of toll-like receptor activity

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Metformin has been demonstrated to possess cardioprotective properties in ischemia/reperfusion conditions. In this study, we hypothesized that a short term treatment with metformin protects infarcted myocardium by suppression of inflammatory responses through AMP-activated protein kinase (AMPK) activation. Male wistar rats were randomly assigned to 6 groups (n=6) of control, sham, isoproterenol (Iso), and treatment with 25, 50, and 100 mg/kg of metformin twice daily for two days concurrent with MI induction. A subcutaneous injection of Iso (100 mg/kg/day) for 2 consecutive days was used to induce myocardial infarction (MI). Ordinary ANOVA with Student-Newman-Keuls post hoc test was used to compare the groups. Iso caused ST-segment elevation in electorcardiogram (ECG), left ventricular dysfunction, intensive myocardial fibrosis along with a profound increase in myocardial myeloperoxidase (MPO) activity and an increase in the serum levels of tumor necrosis factor-alpha (TNFα) and interleukin-6 (IL6). All doses of metformin significantly amended the ECG pattern and improved the left ventricular systolic pressure, contractility and relaxation ($p<0.01$; $p<0.001$). Interstitial fibrosis significantly was attenuated in treated groups compared with control MI group (score: 1.25±0.47 with 50mg/kg metformin versus 3.5±0.28; $p<0.001$). Treatment with metformin (50 mg/kg) also reduced inflammatory responses as indexed by reduced serum levels of TNFα (52%; $p<0.01$) and IL6 (67%; $p<0.01$) as well as by reduced myocardial MPO activity (24%; $p<0.01$). Metformin at 100mg/kg significantly upregulated the level of phosphorylated AMPK (165%; $p<0.001$). Metformin treatment was also associated with a reduction ($p<0.01$) of the level of intracellular toll-like receptors (TLRs) adapter protein, MyD88, that was considerably elevated ($p<0.01$) in the myocardium following MI induction. Taking together, isoproterenol induced myocardial infarction was associated with a significant reduction of AMPK phosphorylation along with an increase in TLR activity. Furthermore, AMPK activation by metformin and subsequent suppression of TLR activity can be considered as a mechanism in protecting the infracted heart and may indicate a link between AMPK and TLRs.